SECONDARY NEOPLASIA AND LATE COMPLICATIONS AFTER TRANSPLANTATION

Abstract# 3642 **Poster Board #-Session: 862-III**

How Can We Quantify the Risk of Squamous Cell Cancer (SCC) and Death in Transplanted Versus Non Transplanted Patients with Fanconi Anemia (FA)? Gerard Socie,[1] Philip S. Rosenberg*,[2] Eliane Gluckman,[1] Blanche P. Alter.[2] [1]*Hematology-Transplantation, St Louis Hospital, Paris, France;* [2]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA.*

Objective: To quantify the risks of SCC (head, neck, and upper esophagus) and death in transplanted and non transplanted FA patients.

Data: Follow-up of non transplanted FA patients in the North American Survey (NAS) cohort and transplanted FA patients in the St Louis Hospital (SLH) cohort.

Methods: Lifetime data analysis methods, including Rate Ratio and Cox proportional hazards models with fixed and time-dependent covariates.

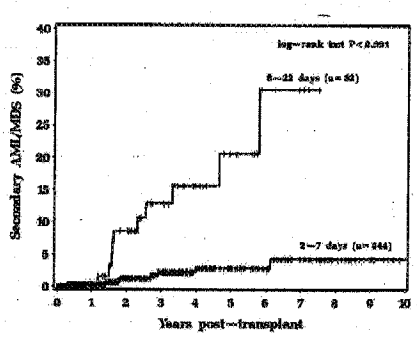
Results: In NAS, 145 non transplanted FA contributed 1,983 person-years, 7 SCC, and 21 deaths. In SLH, 117 transplanted FA contributed 508 person-years, 11 SCC, and 48 deaths. Patients with SCC were younger in SLH than NAS (medians 19 and 33 years, P=0.004). SCC was an adverse risk factor for death, with or without transplant. In non transplanted FA, the risk of death was increased 18-fold subsequent to SCC (P=0.002); in transplanted FA, it was increased 40-fold (P=2*10-7). Transplant increased the age specific risk of SCC by 4.4-fold (P = 0.003). In transplanted FA, acute graft vs. host disease (AGVHD: Grades III+IV vs. None +I+II) increased the risk of SCC by 33-fold (p = 0.006). Chronic graft vs. host disease (CGHVD: limited + extensive vs. none) also increased the risk of SCC - no patient with none had SCC (P=0.018). All other potential risk factors examined, including radiation, were not related to risk of SCC. In transplanted FA patients who survived beyond six months, AGVHD remained a significant risk factor for death (P=3*10-5). Comparing transplanted FA patients who survived beyond six months to non transplanted FA patients of the same age, the subsequent risk of death (all causes) in transplanted FA was 2-fold higher (P=0.017).

Conclusions: Post-transplant, SCC occurs at a higher rate and in younger FA patients. SCC increases the risk of death in transplanted and non transplanted FA. Post-transplant, AGVHD increases the risks of death and SCC. Further studies are needed to eliminate modifiable SCC risk factors.

Abstract# 3643 **Poster Board #-Session: 863-III**

Poor Stem Cell Harvests Increase the Risk of Myelodysplastic Syndrome and/or Acute Myelogenous Leukemia (MDS/AML) Following Autologous Stem Cell Transplant (ASCT). Matt Kalaycio, Lisa Rybicki, Brad Pohlman, Ronald Sobecks, Steven Andresen*, Kristie Summers, Elizabeth Kuczkowski, Brian J. Bolwell. *Bone Marrow Transplant Program, The Cleveland Clinic Foundation, Cleveland, OH, USA.*

From 1/93 through 12/01, we treated 526 patients (pts) for either Non-Hodgkin's Lymphoma (NHL) or Hodgkin Disease (HD) with busulfan, VP-16 , and cyclophosphamide followed by ASCT. Of the 405 pts with NHL, 64% had diffuse large B-cell, 19% had follicular, and 17% had other histologic subtypes of lymphoma. Autologous peripheral stem cells were initially mobilized with either GCSF alone (n = 331), VP-16 plus GCSF (n = 141), or cyclophophamide plus GCSF (n = 2). Poor harvests required additional attempts with VP-16 and/or cyclophosphamide plus GCSF (n = 52). With a median follow-up of surviving patients of 52 months, 18 pts developed MDS/AML confirmed by morphology and/or clonal cytogenetics for an actuarial incidence of 7.9% at 7 years, with a crude rate of 3.4%. Pre-transplant characteristics including age, diagnosis of NHL or HD, bone marrow involvement, prior XRT, previous exposure to chemotherapy, LDH at the time of ASCT, disease status, and method of stem cell mobilization were then analyzed with respect to the subsequent development of MDS/AML. Five univariable risk factors for MDS/AML were identified using Cox analysis: previous exposure to XRT (HR = 4.26, P = 0.003), 4 or more courses of chemotherapy (HR = 5.81, P = 0.002), prior fludarabine exposure (HR = 4.35, P = 0.005), CD34+ cell dose < 2.5 x 10^6/kg (HR = 3.19, P = 0.022), and 8 or more days of pheresis needed to harvest enough stem cells (HR = 7.74, P < 0.001). By multivariable analysis, previous exposure to XRT (HR = 3.60, P = 0.008), 4 or more courses of chemotherapy (HR = 5.61, P = 0.003), and 8 or more days of pheresis needed to harvest enough stem cells (HR = 7.24, P < 0.001) were identified as independent risk factors for MDS/AML.



We conclude that pts who need 8 or more days of pheresis to harvest enough stem cells for ASCT have an increased risk of MDS/AML.

Abstract# 3644 **Poster Board #-Session: 864-III**

Correction of the Fanconi Anemia Phenotype at the Cellular Level Using Hydroxyurea: Implications for Etiopathogenesis and Management after Bone Marrow Transplantation. W.C. Lambert*, Michael Wiederkehr*, Mordechai Tarlow*, Monique M. Brown*. (Intr. by Muriel W Lambert) *Pathology and Laboratory Medicine, UMDNJ-New Jersey Medical School, Newark, NJ, USA.*

Fanconi Anemia (FA) is a complex inherited disease in which patients develop bone marrow failure and/or myelogenous leukemia at an early age. Although bone marrow transplantation (BMT) has been beneficial, a high proportion of these patients go on to develop head and neck cancers and other solid malignancies, regardless of whether BMT has been carried out.. FA is associated with a cell cycle defect in which FA cells fail to arrest or slow their rate of replicative, S-phase DNA synthesis as do normal cells following treatment with a DNA cross-linking agent (CLA). FA cells are also markedly hypersensitive to the clastogenic and cytotoxic effects of such CLAs, characteristics used to define the disease in the diepoxybutane, or DEB test. We wished to test whether, if the cell cycle defect were corrected by treating the cells with an inhibitor of DNA synthesis, the cytoclastic and cytotoxic effects of a CLA, psoralen plus ultraviolet A light (PUVA), would be affected in FA cells. Among DNA synthesis inhibitors, we were particularly interested in examining hydroxyurea (HU), because it has been used successfully to treat other blood diseases, such as sickle cell anemia. Following treatment with PUVA, normal (two cell lines) and FA cells (two FA-A, one FA-C and one FA-G lines) were either mock treated or treated with an inhibitor of DNA synthesis (high dose thymidine, methotrexate, or HU) for 24 hours. Chromosome breaks and both short term (trypan blue exclusion) and long term cell viability (colony forming ability) were then measured. Except for one FA-A cell line that had low thymidine kinase activity, and therefore did not respond to thymidine, all FA cell lines showed dramatic reductions in clastogenicity and increases in viability following PUVA and treatment with any of the DNA synthesis inhibitors. Normal cells failed to show a comparable response. These results indicate that the S-phase cell cycle defect is important in the etiopathogenesis of FA. They also suggest at least one possible mode of therapeutic intervention, prophylactic treatment of FA patients with HU to prevent or delay onset of complications including bone marrow failure, leukemia, or, particularly in patients who have undergone BMT, head, neck, and other tumors.

Abstract# 3645 **Poster Board #-Session: 865-III**

Secondary Leukemia (sL) after Multiple High-Dose Chemotherapy (HDCT) with Peripheral Blood Stem Cells (PBSC) Reinfusion for High Risk Breast Cancer (HRBC) Patients (pts). Saverio Cinieri, Emilia Cocorocchio*, Pier F. Ferrucci*, Fedro A. Peccatori*, Cristina Rabascio*, Alessandra Alietti*, Daniele Laszlo*, Giulio Giordano*, Alberto Agazzi*, Rocco Pastano*, Anna Vanazzi*, Francesco Bertolini, Giancarlo Pruneri*, Aron Goldhirsch*, Giovanni Martinelli. *Hematoncology Division, Internal Medicine Dpt, European Institute of Oncology, Milano, Italy.*

The clinical results of HDCT in the treatment of adjuvant HRBC pts is still controversial. One important issue is the risk of acute and late toxicities. Many authors report an increase of MDS/Leukemia ranging from 1% to 7%. From 1995 we performed HDCT adjuvant in 253 patients. All 253 pts included in this retrospective analysis received multiple HDCT (3 cycles) followed by PBSC reinfusion according to 3 different protocols. Sixty seven pts received multiple HDCT with epirubicin (200 mg/m^2 day 1) and cyclophosphamide (4 g/m^2 day 1) x 3 cycles every 28 days and filgrastim mobilized PBSC reinfusions, one hundred fourteen pts received HD-TEC, the same schedule with the addition of docetaxel (85 mg/m^2 day 1). Seventy-two pretreated antracycline-containing regimen pts, were treated with HD-ICE or T-ICE. All 72 pts received at least 2 cycles of antracycline-containing CT for breast tumors as neoadjuvant CT and presented tumor persistence after surgery, 40 pts received 3 further courses of ifosfamide (2,5 g/m^2 day 1⇒ 4), carboplatin (300 mg/m^2 day 1⇒ 4) etoposide (300 mg/m^2 day 1⇒ 4), 32 pts received the same regimen with docetaxel, 85 mg/m^2 day 1. Radiotherapy (RT) was delivered according to internal guidelines, considering the local extension of the tumor (T3-T4) and the extracapsular invasion of lymph nodes, when indicated RT was administered on chest wall or residual breast, axillary and supraclavicular region for a total of 50 Gy + 10 Gy boost on primary tumor site. All pts suitable for endocrine treatment received tamoxifen 20 mg daily for 5 years. After a median follow-up of 40 months (range 10-114) we observed 3 sAcuteL (1 AML, 1 ALL and 1 T Lymphoblastic NHL). A 42 year old patient (pt) developed an AML (M4 FAB) 16,5 months after the end of HD-EC treatment, cytogenetics findings shown t (9;11). Pt received induction treatment for AML (idarubicin and ARA-C) and after an initial response developed an early relapse resistant to further treatment, she died 11 months after the diagnosis.The 2nd 40 year old pt, 8 months after the end of HD-TEC, developed an ALL pro B positive for (4;11) (q21;q23) and fusion transcript at PCR evaluation, i(7)(q10). The pt was treated with regimen for ALL and died 7 months after the diagnosis in PD. The leukapheresis performed at breast cancer diagnosis, evaluated retrospectively, were negative for (4;11) (q21;q23) fusion transcript. The 3rd 51 year old pt, 5 years after the treatment with 3 HD-ICE , developed a Stage I A mediastinal bulky, T cell lymphoblastic lymphoma, resistant to conventional CT, the pt died of lymphoma 11 months after the diagnosis. All these pts had receive RT after HD-CT. Cytogenetic findings are showed a relationship between the CT and sL, related to HD alkylating agents and etoposide. Concomitant administration of RT and CT, enhances the risk of secondary leukemia, in fact no hematological disorders occurred in the patients who had not received both modalities.Our retrospective analysis confirmed the low short risk of sL after HDCT for HRBC pts. In fact the time to development of such hematological disorders was 8 nd 16,5 months after the end of treatment. Since the possible development of sL and solid tumors may occurred after 10-15 years, longer follow up will be guaranteed to estimate also the long term risk of secondary neoplasia..